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Clinico-pathological factors and [^{18}F]FDG PET/CT metabolic parameters for prediction of progression-free survival in radioiodine refractory differentiated thyroid carcinoma

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Abstract

Objective Identifying prognostic markers for clinical outcomes is crucial in selecting appropriate treatment options for patients with radioiodine-refractory (RAI-R) differentiated thyroid carcinoma (DTC). The aim of this study was to investigate the prognostic value of clinico-pathological features and semiquantitative [^{18}F]FDG PET/CT metabolic parameters in predicting progression-free survival (PFS) in DTC patients with RAI-R.

Patients and methods This prospective cohort study included 110 consecutive RAI-R DTC patients who were referred for [^{18}F]FDG PET/CT imaging. The lesion standard uptake values (SUV)s, including SUVmax, SUVmean, SULpeak as well astotal metabolic tumor volume (tMTV)and total lesion glycolysis (tTLG) were measured. Disease progression was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and/or Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0. PFS curves were plotted using Kaplan–Meier analysis. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors for PFS.

Results [^{18}F]FDG PET/CT metabolic parameters demonstrate predictive value for PFS in RAI-R DTC patients, with sensitivity ranging from 70.7% to 81% and specificity from 75% to 92.3% ($p < 0.001$). PFS was significantly worse in patients with SUVmax > 6.39 g/ml, SUVmean > 3.68 g/ml, SULpeak > 3.14 g/ml, tTLG > 4.23 g/ml × cm^3, and tMTV > 1.24 cm^3. Clinico-pathological factors including age > 55, aggressive variant and follicular histological subtype, extra-thyroidal extension of the primary tumor, stage III – IV disease at initial DTC diagnosis, distant metastases detected on [^{18}F]FDG PET/CT, and metabolic parameters of [^{18}F]FDG PET/CT associated with PFS in univariate analysis ($p < 0.01$). In multivariate analysis, extra-thyroidal extension (HR: 2.25; 95% CI: 1.22 – 4.16; $p = 0.01$), distant metastases on [^{18}F]FDG PET/CT (HR: 2.98; 95%CI: 1.62 – 5.5; $p < 0.001$), and tMTV > 1.24 cm^3 (HR: 4.17; 95% CI: 2.02 – 8.6; $p < 0.001$), were independent prognostic factors for PFS.

Conclusions In addition to classic clinico-pathological factors, the semiquantitative [^{18}F]FDG PET/CT metabolic parameters can be utilized for dynamic risk stratification for progression in RAI-R DTC patients. Furthermore, extra-thyroidal extension of the primary tumor, distant metastases, and tMTV > 1.24 cm^3 are independent prognostic factors for PFS.

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Keywords Radioiodine-refractory differentiated thyroid cancer, [^{18}F]FDG PET/CT, Semiquantitative [^{18}F]FDG parameters, TLG, MTV, Progression-free survival

Introduction

Differentiated thyroid cancer (DTC) is the most common type of endocrine malignancy, generally associated with a favorable prognosis [1, 2]. Current prognostic variables for DTC at initial diagnosis include the patient's age, gender, extrathyroidal extension (ETE) of the primary tumor, clinical stage, presence of regional and distant metastases, histopathological subtype, radioactive iodine avidity, and thyroglobulin levels following thyroidectomy [3]. However, there are no standardized prognostication algorithms for when metastases are diagnosed later, particularly for radioiodine-refractory (RAI-R) patients [4]. This leads to limited management and treatment options that can greatly impact patients' quality of life. A monitoring approach is recommended for asymptomatic patients with stable or slowly progressive RAI-R metastatic DTC to minimize unnecessary treatment. Targeted treatment with multikinase inhibitors should be considered if there is evidence of tumor progression and/or if metastases pose a threat and focal treatment is not feasible [5]. However, 64 – 85% of RAI-R patients treated with targeted therapy with multikinase inhibitors experience grade 3 or higher adverse events [6]. Therefore, identifying prognostic markers for clinical outcomes is essential to choose appropriate treatment options for RAI-R DTC patients.

In the past decades, [^{18}F]FDG PET/CT has emerged as a more valuable diagnostic tool compared to conventional imaging for detecting and localizing recurrence and metastasis with high sensitivity and specificity [7–10]. Recently, a systematic review by Wang H et al. suggested that specific semiquantitative parameters derived from [^{18}F]FDG PET/CT, such as standard uptake value (SUVmax, SUVmean, SULpeak), metabolic volume (MTV), and total lesion glycolysis (TLG), either alone, could serve as prognostic markers for predicting poor outcomes in metastatic DTC [11]. Total metabolic tumor volume (tMTV) and total lesion glycolysis (tTLG) are crucial parameters for evaluating tumor burden and have been extensively studied for predicting disease progression in RAI-R DTC patients [12]. Additionally, a recent study concluded that tTLG and tMTV were only the independent factors associated with overall survival (OS) in DTC patients with elevated thyroglobulin levels and negative [^{131}I] whole-body scans [13]. However, previous studies are primarily retrospective, with limited patient numbers and follow-up durations. Additionally, the measurement of semiquantitative [^{18}F]FDG PET/CT parameters varies among different PET centers due to the lack of standardized measurement methods, imaging protocols, and PET/CT systems. Therefore, our prospective study aims to evaluate the prognostic value of clinico-pathological features and semiquantitative metabolic parameters of [^{18}F]FDG PET/CT in predicting progression-free survival of DTC patients with RAI-R.

Patients and Methods

Patient population

A prospective study was conducted on RAI-R DTC patients at the Department of Nuclear Medicine, Hospital 108, who underwent [^{18}F]FDG PET/CT imaging from January 2016 to December 2022. All patients underwent every 3—12 months follow-up after total thyroidectomy and radioiodine (RAI) therapy. A total of 188 post-operative DTC patients with elevated thyroglobulin (Tg) levels > 10 ng/mL and negative whole-body scan after RAI therapy were indicated for [^{18}F]FDG PET/CT to detect recurrent or metastatic lesions. We identified 122 patients (64.9%) with recurrent/metastatic lesions on [^{18}F]FDG PET/CT findings confirmed by cytology or histopathology, or disease progression on diagnostic imaging. Twelve patients were excluded from the study due to lack of regular follow-up. Ultimately, 110 RAI-R DTC patients with recurrent /metastatic lesions detected on [^{18}F]FDG PET/CT findings were included in the study (Fig. 1).

Clinical and pathological factors

Post-operative DTC patients were recorded for clinical characteristics such as age, gender, invasive features of the primary tumor (T stage), and restaging before the PET/CT scan according to the American Joint Committee on Cancer 8th edition (AJCC 8th) [14]. Histopathological classification was performed according to the 2017 WHO standards [15]. Serum Tg and anti-Tg levels were measured using the Elecsys 2010 immunoassay analyzer (Roche, Switzerland) by electrochemiluminescence immunoassay. Stimulated Tg was measured after thyroid hormone (levothyroxine) withdrawal for 4 weeks (triiodothyronine could be used for the first 2 weeks), with TSH levels reaching ≥ 30 μUI/ml.

[^{18}F]FDG PET imaging and semiquantitative assessment

All RAI-R DTC patients underwent whole-body [^{18}F] FDG PET/CT scan at the Department of Nuclear Medicine, Hospital 108 for detecting recurrent and/or metastatic lesions. The PET/CT imaging was performed by

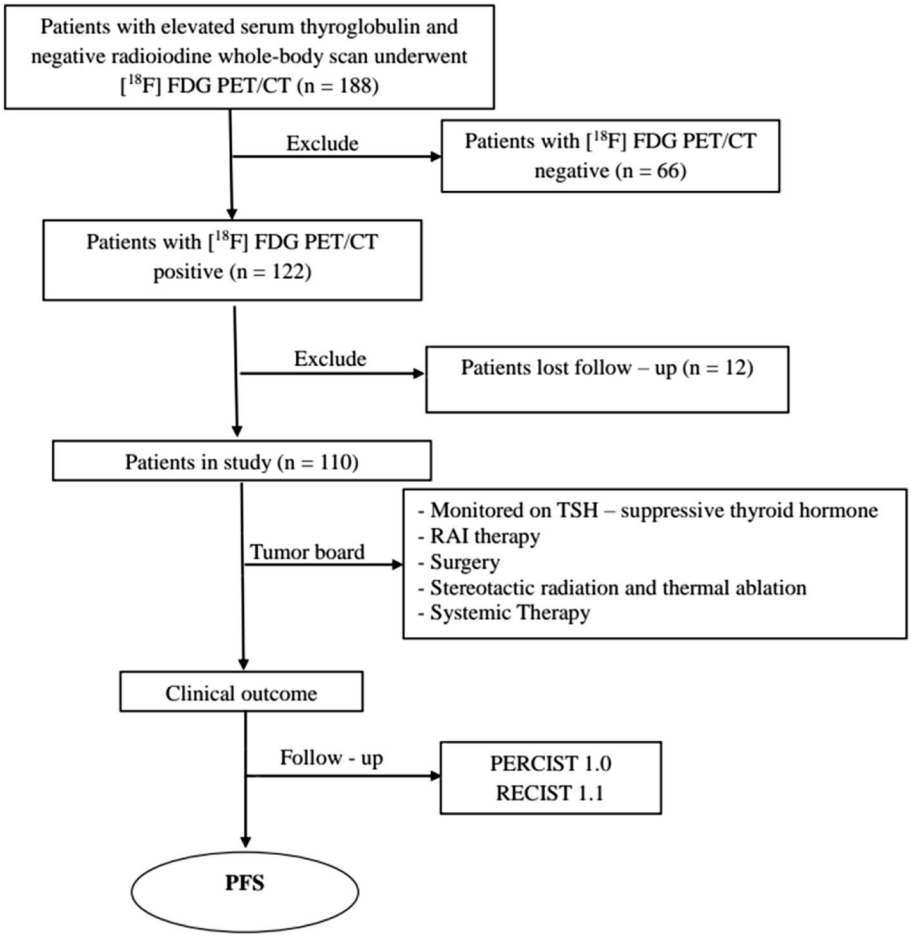


Fig. 1 Flowchart of DTC patients enrolled in this study

GE Discovery 710 system (GE Healthcare, Milwaukee, WI, USA) in accordance with the European Association of Nuclear Medicine (EANM) guidelines, version 2.0 [16]. Each patient fasted at least 6-h before PET/CT scan with a blood glucose level below 150 mg/dL. An intravenous injection of 2.5 MBq/kg body weight (± 10%) of [^{18}F]FDG was administered, and scans were performed approximately 60 ± 10 min post-injection, covering from the skull base to the mid-thigh. PET images were obtained using a three-dimensional mode, using 6-8 bed positions, each scanned for 1.5 minutes. The transaxial field of view (FOV) was set at 70 cm, utilizing iterative reconstruction with 20 subsets/2 iterations and a matrix size of 256×256. The low-dose CT scan without contrast enhancement, the parameters were set as follows: 120 kVp, modulated mAs, a helical slice thickness of 3.75 mm, and 0.5 s/rotation. PET images were reconstructed using an iterative algorithm with attenuation correction based on the CT scan. [^{18}F]FDG PET/CT images were displayed in the trans-axial, sagittal, and coronal planes using the PET OncoViewer, GE workstation (version 4.7, GE Healthcare). [^{18}F]FDG PET/CT images were independently reviewed by two experienced nuclear medicine physicians who were well-informed about the patient's clinical histories. In cases of disagreement, a third expert was consulted to achieve consensus. Any focal tracer uptake exceeding physiological background activity and demonstrating higher activity than the surrounding tissue was deemed indicative of disease [17, 18]. These PET/CT findings were then compared with a reference standard (cytological/histopathologic reports as well as subsequent imaging studies such as ultrasound, contrast CT, MRI, and/or PET/CT), comprising a combination of clinical and/or imaging follow-up spanning at least 6 months.

The volume of interest (VOI) was placed adjacent to physiological [^{18}F]FDG-avid structures on attenuation-corrected PET images using the AW workstation version 4.7 (GE Healthcare, Milwaukee, WI, USA). Subsequently, the region of interest (ROI) within the lesions was evaluated with consideration given to CT imaging. The tumor volume was determined through iterative

adaptive threshold segmentation provided by the vendor (PETVCAR software, GE Healthcare). This algorithm utilized a gradient vector slope approach to determine a threshold value that differentiates the tumor from surrounding tissues, with the SUV maximum value within the bounding box being weighted by a 'w' factor (where $0 \leq w \leq 1$, defaulting to 0.5). The tumor border was automatically contoured, and the metabolic tumor volume (MTV) was derived as the tumor volume. SUVmax and SUVmean were defined as the maximum and average SUV values within the tumor volume, respectively. SULpeak represented the average SUV within a 1 cm^3 spherical region centered on the hottest point within the tumor. Total lesion glycolysis (TLG) was calculated as the product of SUVmean and MTV. Each lesion's metrics are recorded, followed by calculating the SUVmax, SUVmean, SULpeak of the highest lesion, as well as total MTV (tMTV) and total TLG (tTLG) across all [^{18}F]FDG-avid metabolic lesions.

Follow-up, treatment and clinical outcome evaluation

After the PET/CT scan, the multidisciplinary thyroid tumor board convened to determine the appropriate management strategy and treatment for each patient: (1) empirical RAI treatment or TSH suppression therapy with subsequent monitoring for small or slow-progressing lesions; (2) surgery or radiotherapy for localized progressive lesions; (3) systemic therapy (targeted therapy) for multiple lesions that were symptomatic, compressive, life-threatening, or rapidly progressing [3, 5, 19]. All patients underwent periodic followed-up every 3–12 months, which included clinical examination, serum Tg and anti-Tg levels, neck ultrasound, CT and/or MRI, [^{18}F]FDG PET/CT. Disease progression was evaluated using RECIST 1.1 and/or PERCIST 1.0 criteria [20, 21]. The study's endpoint was progression-free survival (PFS) defined as the time from study entry to disease progression or death.

Statistical analysis

Commercial software packages such as SPSS v.25.0 (IBM Corp) were employed for statistical analysis. Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables showing normal distribution were assessed using paired Student t-tests or repeated measure ANOVA. Variables that did not follow a normal distribution were compared using the Mann–Whitney U test. For assessing the predictive capability of each [^{18}F]FDG PET/CT parameter on PFS, the optimal cutoff value, sensitivity, and specificity were determined using receiver-operating characteristic (ROC) curve analysis, with diagnostic performance evaluated by the area under the curve (AUC). Differences between the areas under the ROC curve were evaluated for statistical significance using the DeLong test. Cox regression analysis was utilized to identify significant parameters predicting PFS. The predictive value of clinical factors and [^{18}F]FDG PET/CT parameters on outcomes was initially assessed using univariate analysis. Variables demonstrating a significance level of $p < 0.2$ in univariate analysis were subsequently included in multivariate analysis, using the backward elimitation method. Estimation of PFS was conducted using the Kaplan–Meier method, with a significance threshold set at $p < 0.05$.

Results

General characteristics of the DTC patients are summarized in Table 1. There were 110 RAI-R DTC patients, male-to-female ratio of 1:5.5. Histological subtypes included papillary thyroid carcinoma (87.3%), follicular thyroid carcinoma (10%), and aggressive papillary variants (2.7%). The median stimulated Tg level before the PET/CT scan was 177.9 ng/mL (range: 10.7 – 5982). The median follow-up time was 40 months (range: 1.57 – 82.5 months), during which 52.7% of these patients experienced disease progression following the PET/CT scan.

The most common site of metastases detected by [^{18}F]FDG PET/CT imaging was cervical lymph nodes, observed in 85 out of 110 patients (77.3%), followed by lung metastases with (25.5%), mediastinal lymph node metastases (20.9%), bone metastases (10%), and other sites. The local recurrence in thyroid bed had occurred in 15.5% of patients. Following PET/CT scans, 45 out of 110 patients (40.9%) underwent surgery, while 41 patients (37.3%) were under active surveillance.

A comparison of the AUC for metabolic parameters revealed that tMTV and tTLG exhibited significantly higher predictive values for progression compared to SUVmax, SUVmean, and SULpeak (DeLong test, $p < 0.05$, Fig. 2). The [^{18}F]FDG PET/CT metabolic parameters demonstrate predictive value for disease progression in RAI-R DTC patients with sensitivity ranging from 70.7% to 81% and specificity from 75% to 92.3% ($p < 0.001$). Notably, tTLG and tMTV showed the highest specificity among these parameters (92.3%; 90.4%, respectively).

The median PFS for RAI-R DTC patients was 40.57 months, with a 5-year PFS rate of 31.3%. There was a statistically significant correlation between the [^{18}F]FDG metabolic parameters and PFS ($p < 0.001$, Fig. 3). The rate of PFS within 5-year of follow-up were significantly lower in groups with SUVmax > 6.9 g/ml, SUVmean > 3.68 g/ml, SULpeak > 3.14 g/ml, tTLG > 4.23 g/ml x cm^3, and tMTV > 1.24 cm^3 than in remaining groups ($p < 0.001$). Clinico-pathological factors such as age > 55, aggressive variant and follicular histological subtype, ETE of the primary tumor, stage III – IV disease at initial DTC

Table 1 General characteristics of RAI-R DTC patients

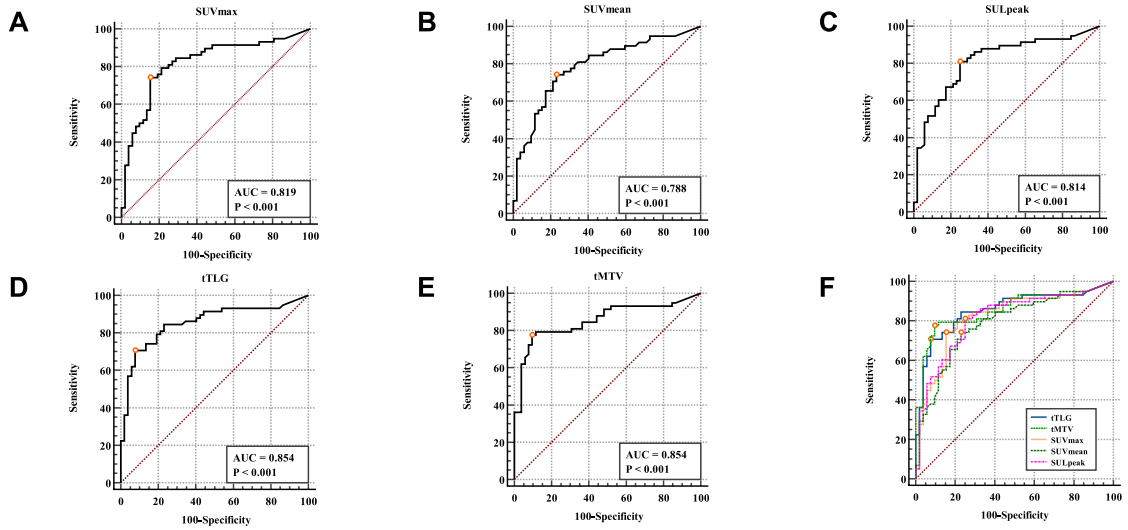
Characteristics		Number (%)
Age	< 55	54 (49.1%)
	≥ 55	56 (50.9%)
	Mean ± SD (min – max)	53.6 ± 14.25 (17 – 79)
Gender	Male	17 (15.5%)
	Female	93 (84.5%)
	Female/Male ratio	1/5.5
Histological subtype	Papillary	96 (87.3%)
	Aggressive variant and follicular	14 (12.7%)
ETE of the primary tumor	No	73 (66.4%)
	Yes	27 (24.5%)
	No determined	10 (9.1%)
Stage at initial DTC diagnosis	I – II	80 (72.7%)
	III—IV	27 (24.6%)
	No determined	3 (2.7%)
Cumulative RAI activities administrated (mCi)	≤ 600	94 (85.5%)
	> 600	16 (14.5%)
	Mean ± SD	405 ± 228.8 (80 – 1300)
Number of ^{131}I therapy course (s) before [^{18}F]FDG PET/CT		2.97 ± 1.44 (1 – 8)
Stimulated serum Tg before [^{18}F]FDG PET/CT (ng/ml) (median, range)		177.9 (10.7 – 5982)
Metabolic parameters of [^{18}F]FDG PET/CT (median, quartiles)	SUVmax (g/ml)	6.39 (3.24 – 11.62)
	SUVmean (g/ml)	3.68 (2.39 – 6.07)
	SULpeak (g/ml)	3.14 (1.89 – 7.19)
	TLG (g/ml x cm^3)	4.23 (0.93 – 23.54)
	MTV (cm^3)	1.24 (0.34 – 4.95)
Median of follow up (months)		40 (6.57 – 82.5)
Progressive disease		58 (52.7%)

diagnosis, distant metastases on [^{18}F]FDG PET/CT findings, and [^{18}F]FDG PET/CT metabolic parameters higher than median are predictors for PFS in univariate analysis (Table 2). Multivariate analyses showed ETE of the primary tumor, distant metastases on [^{18}F]FDG PET/CT findings and tMTV > 1.24 cm^3 are the independent factors in predicting PFS ($p < 0.01$). A representative case is shown in Fig. 4.

Discussion

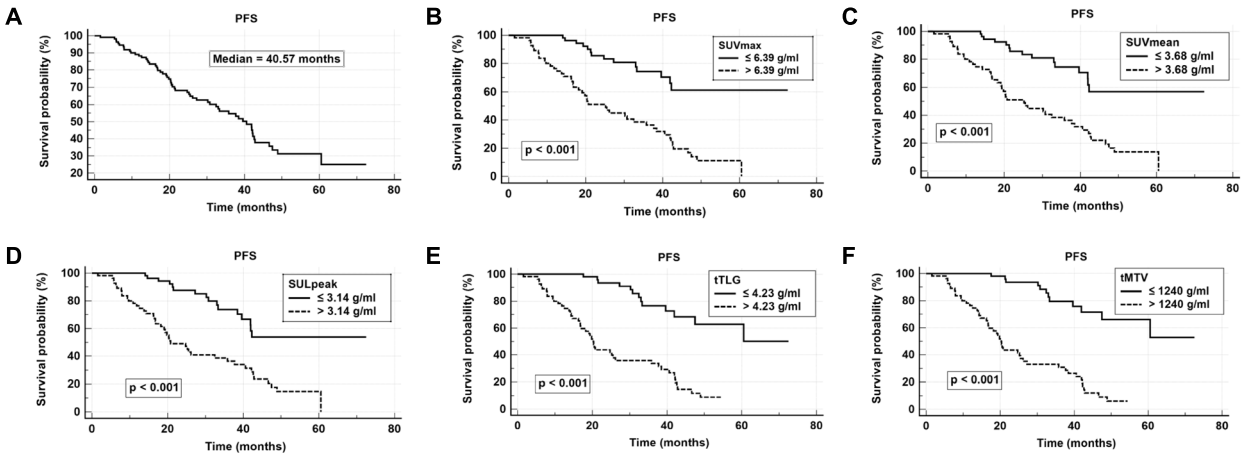
DTC patients exhibit favorable prognoses, particularly when managed with surgery, thyroid hormone therapy, and RAI treatment [3, 22]. Nonetheless, 10—30% of DTC patients develop distant metastases—a key adverse prognostic factor significantly impacting survival and disease progression in post-surgical cases. The incidence of distant metastases escalates in RAI-R metastatic DTC, where median survival plummets to a mere 3—5 years [23, 24]. While identifying predictors of clinical outcomes in RAI-R DTC patients is critically important, consensus on specific prognostic factors for RAI-R cases remains elusive. The strengths of our study are the large cohort of patients and its prospective design.

Our prospective study included 110 RAI-R DTC patients, with a median follow-up time of 40.57 months (range: 6.57—82.5 months). During this period, the progression rate was 52.7%. These findings are consistent with the median of PFS estimated in the literature (2, 16). The high rate of disease progression in patients with RAI-R can be explained by the more dedifferentiated in the [^{18}F]FDG negative/RAI positive group compared to the [^{18}F]FDG positive/RAI positive group (20). Our findings align with previous literature on the poor prognosis for [^{18}F]FDG-avid lesions in patients with RAI-R, showing a 5-year PFS probability of 31.3%. This supports the hypothesis that [^{18}F]FDG positivity in can act as a prognostic marker by identifying the imaging phenotype of DTC patients with aggressive disease. The advantage of [^{18}F]FDG-PET in detection of phenotypical aggressive tumor types help to identify patients who would benefit from surgical resection or early initiation of tyrosine kinase inhibitor therapy.



	AUC	95% CI	p	Cut-off	Youdens Index	Se	Sp	NPV	PPV	Acc
SUVmax (g/ml)	0.819	0.73 – 0.89	< 0.001	7.04	0.5875	74.1	84.6	74.5	80	77.3
SUVmean (g/ml)	0.788	0.7 – 0.86	< 0.001	3.68	0.5106	74.1	76.9	72.7	78.2	75.5
SULpeak (g/ml)	0.814	0.73 – 0.88	< 0.001	2.83	0.5603	81	75	70.9	76.4	73.6
tTLG (g/ml x cm^3)	0.854	0.77 – 0.91	< 0.001	8.95	0.63	70.7	92.3	76.4	81.8	79.1
tMTV (cm^3)	0.854	0.77 – 0.91	< 0.001	1531	0.6797	77.6	90.4	78.2	83.6	80.9

Fig. 2 AUC and ROC curve of [^{18}F]FDG PET/CT metabolic parameters's value in predicting PFS



	SUVmax (g/ml)		SUVmean (g/ml)		SULpeak (g/ml)		tTLG (g/ml x cm^3)		tMTV (cm^3)	
	≤ 6.39	> 6.39	≤ 3.68	> 3.68	≤ 3.14	> 3.14	≤ 4.23	> 4.23	≤ 1240	> 1240
5-year PFS	61.2 %	11.2 %	56.9 %	13.8 %	53.8 %	14.7 %	62.7 %	8.8 %	66 %	6 %

Fig. 3 The Kaplan-Meier curves illustrate the relationship between [^{18}F]FDG PET/CT metabolic parameters and PFS

The refractory to RAI therapy has become the main cause of disease-specific death, with a low survival rate due to limited therapeutic options [23, 25, 26]. Hence, the significant role of prognostic factors in predicting PFS is beneficial for optimizing treatment indications and improving clinical outcomes in clinical practice [27]. The

Table 2 Univariate and multivariate cox analysis of clinico-pathological and semiquantitative [^{18}F]FDG PET/CT Metabolic Parameters for PFS

Parameters	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age ≥ 55	5.34	2.86 – 9.97	0.000*	1.63	0.67 – 3.93	0.28
Male	1.0	0.5 – 1.97	0.98	-	-	-
Aggressive variant and follicular histological subtype	3.81	1.96 – 7.41	0.000*	1.28	0.49 – 3.3	0.617
ETE of primary tumor	2.18	1.2 – 3.9	0.01*	2.25	1.22 – 4.16	0.01*
Stage III-IV at DTC diagnosis	4.98	2.85 – 8.72	0.000*	1.16	0.48 – 2.78	0.741
Cumulative RAI activities administrated > 600 mCi	1.74	0.9 – 3.38	0.1	-	-	-
Stimulated Tg > 177.9 ng/ml	1.55	0.91 – 2.64	0.108	-	-	-
Thyroid beds	1.3	0.68 – 2.48	0.421	-	-	-
Cervical lymphnode metastases	0.64	0.36 – 1.12	0.118	-	-	-
Distant metastases on [^{18}F]FDG PET/CT findings	5.19	2.99 – 9.0	0.000*	2.98	1.62 – 5.5	0.000*
SUVmax > 6.39 (g/ml)	4.4	2.4 – 8.04	0.000*	1.63	0.43 – 6.18	0.475
SUVmean > 3.68 (g/ml)	3.87	2.14 – 6.98	0.000*	0.62	0.12 – 3.23	0.571
SUVpeak > 3.14 (g/ml)	3.71	2.08 – 6.62	0.000*	1.43	0.4 – 5.07	0.58
tTLG > 4.23 (g/ml x cm^3)	5.93	3.13 – 11.2	0.000*	1.66	0.47 – 5.88	0.43
tMTV > 1.24 (cm^3)	7.26	3.74 – 14.1	0.000*	4.17	2.02 – 8.6	0.000*

(*): statistical significance

prognostic values of clinical and pathological factors at the time of diagnosis are still in debate. A retrospective study of 153 patients with RAI-R indicated no significant association between gender, initial stage, histological subtype and clinical outcomes [28]. In another studies, the T stage showed a greater propensity for developing distant metastases, age, initial DTC stage, and histology correlated with clinical outcomes in univariate analysis, but only age remained a strong predictor of survival in multivariate analysis [29, 30]. Our present study shows that age > 55, aggressive variant and follicular histological subtype, ETE of the primary tumor, stage III—IV disease at initial DTC diagnosis were associated with PFS. Notably, ETE of the primary tumor is an independent prognostic factor in predicting disease progression in RAI-R DTC patients. The differences in the prognostic value of clinical histological factors are likely due to the versions of AJCC/TNM and treatment options implemented.

The presence of distant metastases significantly affects survival and plays a crucial role in the TNM staging systems. Moreover, [^{18}F]FDG uptake of metastatic lesions was known to be poor prognostic factors for distant metastatic thyroid cancer in previous studies [31–34]. Our finding indicates that distant metastates detected by [^{18}F]FDG PET/CT serves as a strong prognostic factor in predicting PFS in RAI-R DTC patients. The advantage of [^{18}F]FDG-PET in detection of phenotypical aggressive tumor types help to identify patients who would benefit from early initiation of tyrosine kinase inhibitor (TKI) therapy.

In present study, the semiquantative [^{18}F]FDG PET/CT metrics we analyzed, SUVmax, SUVmean, SULpeak, tMTV and tTLG were highly correlated with PFS by univariate analysis and tMTV remained predictors of PFS in multivariate. Using the semiquantitative metabolic parameters of tumor burden and biological aggressiveness, [^{18}F]FDG-PET/CT imaging can act as a prognostic biomarker for predicting recurrence and progression in several cancer types [35–37]. Our study illustrates that a tMTV > 1.24 cm^3 is associated with poorer PFS and a higher rate of disease progression over 5—year. MTV represents the tumor burden, and a high overall tumor burden has long been recognized as a factor associated with poor prognosis. However, tTLG was not significantly related to PFS in our study. Additionally, a recent study demonstrated that an MTV threshold of 57 mL and a TLG threshold of 6.3 significantly distinguish between groups in terms of overall survival (OS) and PFS [12]. Interestingly, another study in 37 patients with metastatic DTC noted that only a TLG less than 154 improved PFS in univariate analysis, but not MTV [38]. The variations in the actual measurements of MTV and TLG between studies are likely due to the different tumor segmentation methods used for quantification. Manohar et al.[12] utilized a gradient-based segmentation approach implemented in MIM 6.x software, whereas Masson-Deshayes et al. [38] applied an adaptive segmentation technique using an optimal threshold model adjusted according to the tumor-to-background contrast. In our prospective,

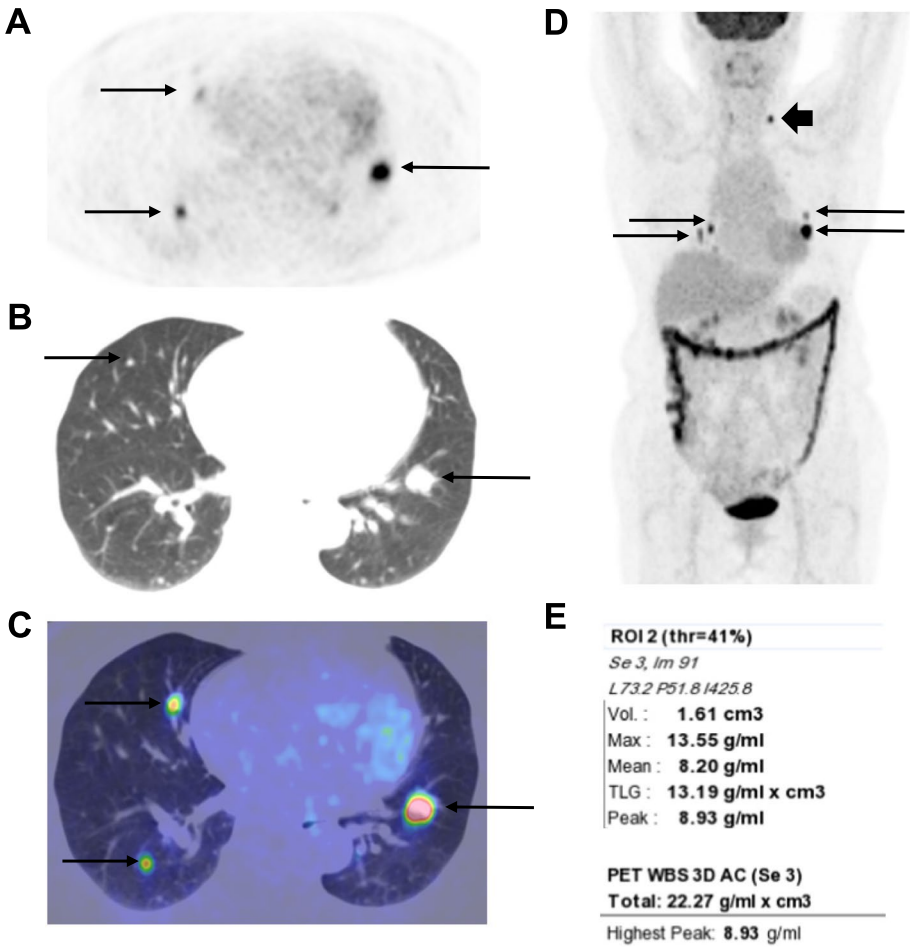


Fig. 4 [^{18}F]FDG PET/CT images showed lesions in RAI-R DTC patients with cervical lymph node and lung metastases. A patient diagnosed with papillary thyroid carcinoma, presenting metastases in the cervical lymph nodes and lungs (pT1N1bM1), underwent four times of RAI therapy, receiving a cumulative dose of 600 mCi. Before the [^{18}F]FDG PET/CT scan, the stimulated Tg level was recorded at 908 ng/ml, and the patient's condition was classified as stage IV according to the AJCC 8th edition. The the [^{18}F]FDG PET/CT images showed lesions in the cervical lymph node metastases (**A**, **B**, **C**, **D** arrows), lung metastases (**D**, block arrow) with SUVmax, SUVmean, SULpeak, tTLG, and tMTV being 13.55 g/ml, 8.2 g/ml, 8.93 g/ml, 22.27 g/ml × cm^3, and 2506 ml, respectively (**E**). After the [^{18}F]FDG PET/CT scan, the patient received systemic treatment with sorafenib, experiencing disease progression after 25.53 months as per PERCIST 1.0 criteria. Subsequently, lenvatinib was administered as continued systemic therapy post-progression

we employed a gradient edge detection algorithm for tumor segmentation, unlike manual tumor segmentation or threshold segmentation methods. Gradient segmentation has been shown to be the most accurate and consistent technique for defining tumor volume [39, 40]. It demonstrates superior correlation and reliability with pathology-based tumor volume compared to threshold segmentation methods [41, 42].

A limitation of this study is the average follow-up time of 40 months, which may be insufficient to evaluate overall survival due to the prolonged progression of recurrent/metastatic RAI-R DTC. Additionally, patient heterogeneity regarding the extent of metastatic lesions and treatment could influence the natural course of the disease. Furthermore, the absence of a radiomics tool in our study is another limitation, which we aim to address in future research.

Conclusions

[^{18}F]FDG PET/CT is a metabolic imaging method that not only has value in detecting recurrences and metastases but also in dynamic risk stratification in DTC patients with RAI-R. Our study suggests that tTLG and tMTV have high specificity for predicting disease progression. Moreover, extra-thyroidal extension of the primary tumor, distant metastases on [^{18}F]FDG PET/CT findings and tMTV are independent prognostic factors. Further prospective studies are needed to explore the relationship between semi-quantitative [^{18}F]FDG metabolic parameters and overall survival in RAI-R DTC patients.

Abbreviations

RAI-R	Radioiodine-refractory
DTC	Differentiated thyroid carcinoma
[^{18}F]FDG PET/CT	[^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography
MRI	Magnetic Resonance Imaging
SUV	Standard Uptake Value
tMTV	Total metabolic tumor volume
tTLG	Total lesion glycolysis
RECIST	Response Evaluation Criteria in Solid Tumors
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumors
PFS	Progression-free survival
[^{18}F]FDG	Fluorine-18 Fluorodeoxyglucose
ETE	Extra-thyroidal extension
AJCC	American Joint Committee on Cancer
WHO	World Health Organization
Tg	Thyroglobulin
TSH	Thyroid-stimulating hormone
EANM	European Association of Nuclear Medicine
FOV	Field of view
VOI	Volume of interest
AUC	Area under the curve

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Clinical trial number
Not applicable.

Authors' contributions
Basic study idea was made by L.N.H; M.H.S and N.T.P conducted patient management and procedures. Data were curated and analyzed by N.T.P and L.N.H, M.H.Th. and validated by L.N.H. Draft of manuscript was written by L.N.H. and N.T.P and reviewed by all authors. M.H.S edited the manuscript.

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Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The study conforms to the ethical guidelines in accordance with the Helsinki Declaration as revised in 2013 and was approved by Hospital 108 review board and ethical committee. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
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The authors declare no competing interests.

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